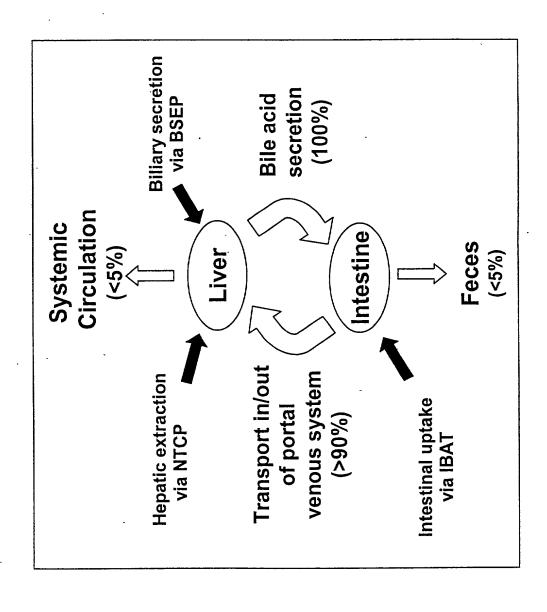
GABA (1)

Figure 2

The Enterohepatic Circulation with Key Transporter Proteins Mediating

Bile Acid Circulation



Bile Acid Conjugates of HMG-CoA Reductase Inhibitor

HR 780

$$R = OH S 3554$$

 $R = NHCH2CO2H S 3898$

$$R = UH S 3334$$

$$R = NHCH2CO2H S 3898$$

 $R = NHCH_2CH_2SO_3H S 4193$

R1 = α -OH; R2 = α -OH (Cholate) R1 = β -OH; R2 = H (Ursodeoxycholate) R1 = α -OH; R2 = H (Chenodeoxycholate) R1 = H; R2 = α -OH (Deoxycholate) R1 = β -OH; R2 = α -OH (Ursocholate) R1 = H; R2 = H (Lithocholate)

$$|| \frac{R^{2}}{R^{1}} || \frac{R^{2}}{R^{2}} || \frac{R^{2}}$$

HOW (XII)
$$SO_3H$$
, $OP(O)(OR^{19})(OH)$,

R1 = α -OH; R2 = α -OH (Cholate) R1 = β -OH; R2 = H (Ursodeoxycholate) R1 = α -OH; R2 = H (Chenodeoxycholate) R1 = H; R2 = α -OH (Deoxycholate) R1 = β -OH; R2 = α -OH (Ursocholate) R1 = β -OH; R2 = α -OH (Ursocholate)

R1 = α -OH; R2 = α -OH (Cholate) R1 = β -OH; R2 = H (Ursodeoxycholate) R1 = α -OH; R2 = H (Chenodeoxycholate) R1 = H; R2 = α -OH (Deoxycholate) R1 = β -OH; R2 = α -OH (Ursocholate) R1 = H; R2 = H (Lithocholate)

$$R1 = \alpha - OH \; ; R2 = \alpha - OH \; (Cholate)$$

$$Y = \alpha - OH \; ; R2 = H \; (Ursodeoxycholate)$$

$$Y = \beta - OH \; ; R2 = H \; (Chenodeoxycholate)$$

$$Y = \alpha - OH \; ; R2 = H \; (Chenodeoxycholate)$$

$$Y = \alpha - OH \; ; R2 = \alpha - OH \; (Ursocholate)$$

$$Y = \beta - NH$$

$$Z = M \quad CO_2H$$

$$Y = \beta - OH \; ; R2 = \alpha - OH \; (Ursocholate)$$

$$Y = \beta - NH$$

$$Z = M \quad SO_3H$$

$$R1 = \beta - OH \; ; R2 = \alpha - OH \; (Ursocholate)$$

(XXVI)

Figure 9: Uptake of (8) (XP10569) or Glycochocholate by **IBAT-Transfected CHO Cells**

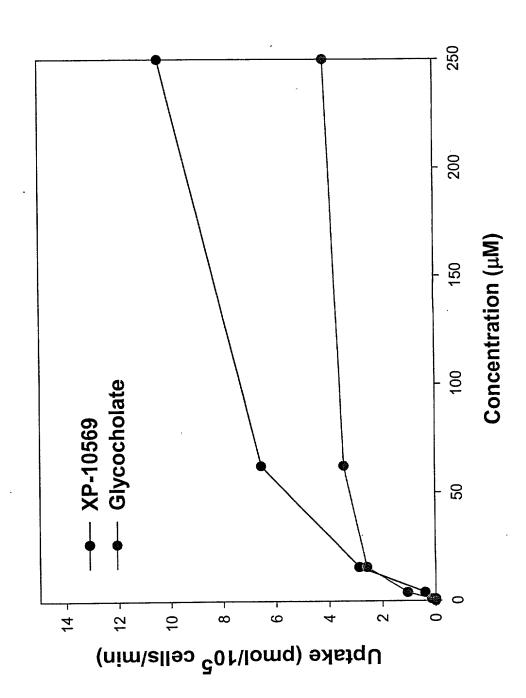
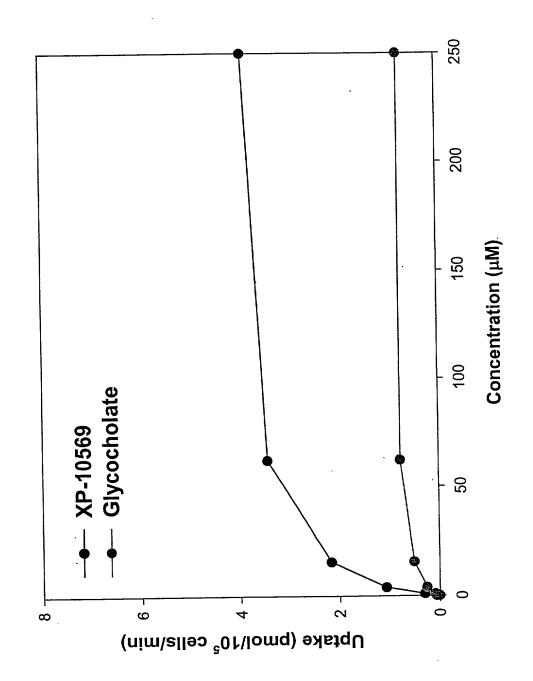
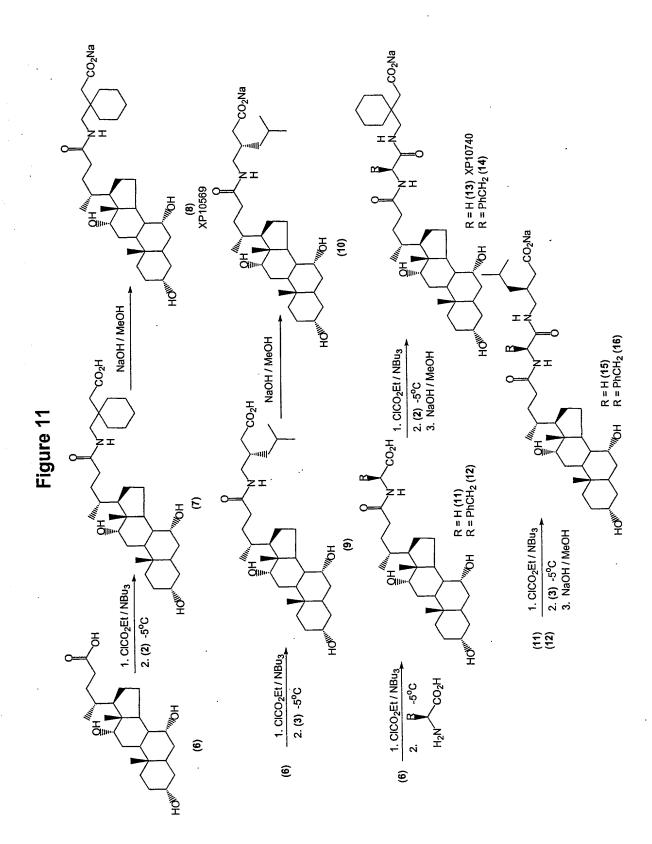


Figure 10: Uptake of (8) (XP10569) or Glycocholate by LBAT-Transfected CHO Cells





(43)

 $2. \, \text{NaN}_3 \, , -5^{0} \text{C}$

(42)

(37)

(25)

ĕ

. P

(51)

(54)

Compounds (92) - (103) prepared following methods described in co-pending application "Bile Acid-Derived Compounds for Enhancing Oral Absorption and Systemic Bioavailability of Drugs" assigned to XenoPort, Inc.

(109) HO

, P P

3α (114) 3β (115)

3. Na⁺ exchange resin H₂O / MeOH

(**96**) or (**97**) 2. TFA

ΙZ

1. 2,4,6-Cl₃C₆H₂C(O)Cl

Et₃N, DMAP

(105)

3. Na⁺ exchange resin H₂O / MeOH 4. H₂ , Pd/C , EtOH 1. CICO₂Et NBu₃ , dioxane 2. Taurine, H₂O (116) 3α (117) 3β (118) NHCBz Figure 25 1. CICO₂Et NBu₃ , dioxane . 3α (119) 3β (120) 2. (2) ,H₂O 돝 BZCHN CBz-Phe 1. 2,4,6-Cl₃C₆H₂C(O)Cl Et₃N, DMAP (**92**) or (**93**) 2. TFA (116)

l. (39) or (43) Toluene, ∆

(2) ,H₂O

CCl4, py

(66) - (96)

resin H₂O / MeOH 3. Na⁺ exchange

R= Na, Y=
$$3\alpha$$
-O (139) R= Me, Y=
R= Na, Y= 3β -O (140) R= Me, Y=
R= Na, Y= 3α -NH (141) R= Me, Y=
R=Na, Y= 3β -NH (142) R=Me, Y=

R= Me, Y=
$$3\alpha$$
-O (143)
R= Me, Y= 3β -O (144)
1) R= Me, Y= 3α -NH (145)
2) R=Me, Y= 3β -NH (146)

(56) (57)

R = H, Y= 3α -O (135) R = Me, Y= 3α -O (139) R= H, Y= 3β -O (136) R= Me, Y= 3β -O (140) R= H, Y= 3α -NH (137) R= Me, Y= 3α -NH (141) R= H, Y= 3β -NH (138) R= Me, Y= 3β -NH (142)

R'= Na, R= H, Y= 3β-O (144) R'= Na, R= H, Y= 3α-NH (145) R'= Na, R= H, Y= 38-NH (146) R'= Na, R = H, Y= 3α -O (143)

R'= Na, R= Me, Y= 3 β -O (148) R'= Na, R= Me, Y= 3 α -NH (149) R'= Na, R= Me, Y= 3 β -NH (150) R'= Na, R = Me, Y= 3α -O (147)

R'= Me, R= H, Y= 3α -NH (153) R'= Me, R= H, Y= 3\bar{154} R'= Me, R = H, Y= 3α -O (151) R'= Me, R= H, Y= 3β -O (152)

R'= Me, R = Me, Y= 3α -O (155) R'= Me, R= Me, Y= 3β -O (156) R'= Me, R= Me, Y= 3α -NH (157) R'= Me, R= Me, Y= 3β -NH (158)

Fmoc-Phe-OH

(66) - (96)

DIC, DMF

(167)

Ž T

H₂, Pd/C, EtOH

(116)

(96) - (99)

2. (167), dioxane, H₂O

3. Optionally CH₂N₂

4. TFA

5. Na⁺ exchange resin

H₂O / MeOH

 4-Nitrophenyl chloroformate R= Na, Y= 3α -O (168) R= Me, Y= 3α -O (172) R= Na, Y= 3β -O (169) R= Me, Y= 3β -O (173) R= Na, Y= 3α -NH (170) R= Me, Y= 3β -NH (174) R= Me, Y= 3β -NH (175)

2. Piperidine, CH₂Cl₂ (for (43))

4. Na⁺ exchange resin

3. TFA

(188) - (195)

1. (39) or (43) Toluene, ∆ H₂O / MeOH

R= Et, Y= 3α-NH (190) R= Et, Y= 3β-NH (191)

R'= Na, R= Et, Y= 3α-O (204) R'= Na, R= Et, Y= 3β-O (205) R'= Na, R= Et, Y= 3α-NH (206) R'= Na, R= Et, Y= 3β-NH (207) R'= Me, R= Bn Y= 3α-O (200) R'= Me, R= Bn Y= 3β-O (201) R'= Me, R= Bn Y= 3α-NH (202) R'= Me, R= Bn Y= 3β-NH (203) R'= Me, R= Et, Y= 3α-O (196) R'= Me, R= Et, Y= 3β-O (197) R'= Me, R= Et, Y= 3α-NH (198) R'= Me, R= Et, Y= 3β-NH (199)

R'= Na, R= Bn Y= 3α-O (208) R'= Na, R= Bn Y= 3β-O (209) R'= Na, R= Bn Y= 3α-NH (210) R'= Na, R= Bn Y= 3β-NH (211)

(96) (94)

HgO , CH₂Cl₂ (215) and (216)

(56) (57)

R'= H, R = H, 3α (221) R'= Me, R = H, 3α (225) R'= H, R= H, 3β (222) R'= Me, R= H, 3β (226) R'= H, R= Me, 3α (227) R'= Me, R= Me, 3β (227) R'= Me, R= Me, 3β (224) R'= Me, R= Me, 3β (228)

9